AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 49:634–641 (2006)

Diachronic Study of Pleural Plaques in Rural Population With Environmental Exposure to Asbestos

L. Sichletidis, MD, FCCP,* D. Chloros, MD, N. Chatzidimitriou, MD, I. Tsiotsios, MD, D. Spyratos, MD, and D. Patakas, MD

Background *The progress of pleural plaques in persons exposed to environmental asbestos in Almopia, Greece were studied prospectively.*

Methods *During a 15-year period, 198 individuals, in whom pleural plaques had been observed during the period 1988–1990 were followed. Respiratory function was initially evaluated in 23. All were inhabitants of seven villages of Northern Greece, where rocks with high concentration in asbestos fibers were used for whitewashing until 1935.*

Results *Out of this population, 126 survived and underwent chest X-ray in 2003 while respiratory function was retested in 18. New radiological findings were compared to previous ones using digital technology. Furthermore, the cause of death of the remaining 72 was recorded. Deterioration of X-ray findings was observed in all survivors. Not only did the surface area of previous plaques increase (8.66 ± 12.6 cm^2, mean value $\pm$ SD) but new ones also appeared. Total lung capacity decreased from 95.6 ± 14.8 in 1998 to 76.5 ± 9.3% predicted in 2003. It was found that out of 72 deaths, 11 people died of malignant lung neoplasm, and 4 of mesothelioma.*

Conclusions *Radiological appearance of pleural plaques and respiratory function of people previously exposed to asbestos environmental pollution worsens over the years. Prevalence of mesothelioma was found to be higher than expected.* Am. J. Ind. Med. 49:634–641, 2006. *© 2006 Wiley-Liss, Inc.*

KEY WORDS: pollution; pleural lesions; tremolite; mesothelioma; respiratory function; Greece

INTRODUCTION

Asbestos fibers and other minerals, when present in certain areas, are mainly to blame for the development of endemic pleural plaques, as illustrated in chest X-ray of the inhabitants of those areas [Hillerdal, 1986]. Mineral fibers when concentrated in traditional materials such as whitewashing were proven to be especially dangerous in Turkey [Baris et al., 1981], in Metsovo in Western Greece [Constantopoulos et al., 1985], as well as in the tested area of Almopia, a county of Pella in Northern Greece [Sichletidis et al., 1992a]. In addition to pleural plaques, a high frequency of mesothelioma has been found to co-exist [Baris et al., 1979; Langer et al., 1987; Sichletidis et al., 1992b].

The present study is part of a three-step research project, taking place during the period 1988–2003 in the region of Almopia, Greece. Cases of malignant mesothelioma and pleural plaques among the inhabitants of Almopia were diagnosed. Subsequently, an environmental study was conducted and showed that concentration of asbestos fibers indoors ranged from 0.01/cm^3 (in old abandoned houses) to 17.9/cm^3 (1 week after brushing a wall with a specific material and then slightly scratching it). Very high concentrations of asbestos fibers, 50–90%, especially chrysotile and

Pulmonary Clinic, Laboratory for the Investigation of Environmental Diseases, Aristotle University of Thessaloniki, Thessaloniki, Greece.

*Correspondence to: L. Sichletidis, Associate Professor of Medicine, G. Papanicolaou Hospital, Exochi, 57010 Thessaloniki, Greece. E-mail: dchloros@msn.com

Accepted 13 April 2006

DOI 10.1002/ajim.20334. Published online in Wiley InterScience (www.interscience.wiley.com)

tremolite, were also found in the rocks in a nearby ravine that the inhabitants had been using as the main source for whitewashing materials until 1935. Consequently, a 28-month observational study was carried out during 1988–1990 in seven villages of Almopia with a total population of 3,901 inhabitants. Prevalence of pleural plaques in individuals over 40 years old in the specific region was found to be 5.2–39.6% [Sichletidis et al., 1992a] which is considered to be very high. The same study had shown high risk of malignant mesothelioma in the inhabitants of this area [Sichletidis et al., 1992b].

The present study was conducted to evaluate the progress of radiological findings as well as the respiratory function of individuals tested 15 years ago and to investigate the cause of death in the group of people who presented with pleural plaques initially.

MATERIALS AND METHODS

During the years 1988–1990, an observational study in seven villages of Almopia (Northern Greece) was conducted. Three thousand nine hundred one inhabitants were asked to participate in the study and 1,086 (818 over the age of 40) accepted. They all underwent chest radiography. Additionally, respiratory function was tested in 23 individuals. Pleural plaques were present in 198 persons over the age of 40 (24.2%), malignant lung neoplasm in 9, and malignant mesothelioma in 5 persons [Sichletidis et al., 1992a,b].

In the present study, the 198 individuals with pleural plaques were followed for 15 years and re-examined in 2003. Out of 198 individuals, 126 survived and consented to postero-anterior chest X-rays. All persons gave their written consent to participate in the survey. Radiological examinations took place at the same laboratory of Health Center in Almopia as the previous survey and films were interpreted by two experienced physicians separately. A triplunix C.G.R-G.E (source distance 1.80 m, K.V 110 and tension MAS 6) was used. Each X-ray was compared to that obtained 15 years ago using digital technology techniques (digital camera, Adobe Photoshop 6) and measurement of pleural plaques' surface area was performed with Auto Cad 2000 Autodesk.

Respiratory function tests were performed in 18 survivors, of the 23 who had been initially examined during the years 1988–1990. All tests were performed in the Pulmonary Function Laboratory of Pulmonary Clinic of Aristotle University of Thessaloniki in the General Hospital "G. Papanicolaou." Type Jaeger spirometer was used and air flow, lung volumes, and capacities were measured by the method of Helium closed circuit. Crapo et al. [1982] predicted values were used.

During the 15-year period, most of the afflicted persons were under supervision by doctors in the Health Center. With the permission of municipality authorities, death certificates were used to retrieve information on the cause of death of the remaining 72 people individuals. None was missed during the follow up. Study design is depicted in Figure 1.

The study protocol has been reviewed and approved by the Scientific Committee of "G. Papanicolaou" Hospital, Thessaloniki.

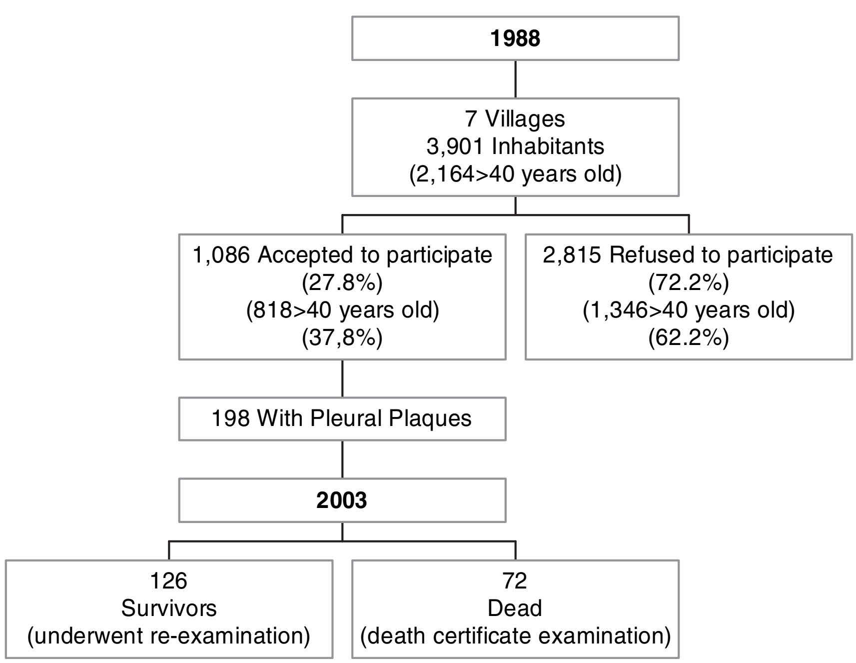


FIGURE 1. Study design.

TABLE I. Measurement of Pleural Plaques' Surface Area in 126 Residents of Almopia, Northern Greece in 1988–1990 and 2003

	1988–1990		2003	
	Mean ± SD (cm^2)	Range (cm^2)	Mean ± SD (cm^2)	Range (cm^2)
Right hemithorax	2.23 ± 3.9	0–16.61	5.39 ± 8.79	0–35.45
Left hemithorax	6.29 ± 8.22	0–30.5	11.79 ± 14.03	0.46–52.15
Total	8.52 ± 11.4	0.38–47.11	17.18 ± 19.24	0.46–69.59

RESULTS

Radiological Outcome

Comparing 1988–1990 to 2003 chest X-rays of the 126 survivors, it was obvious that the surface area of pleural plaques had been increased and new ones had appeared. The mean values ± SD for plaques surface area was 8.52 ± 11.4 cm^2 on first examination (1988–1990) and increased to 17.18 ± 19.24 cm^2 in 2003 (Table I). The total area of pleural plaques increased from 1,073.4 cm^2 to 2,164.5 cm^2. Consequently, after 15 years, the total area difference amounted to 1091.1 cm^2 (Figs. 2–4). No radiologic sign of parenchymatous damage was observed. In the first measurement, the total area of plaques was 792.1 cm^2 on the left and 281.3 cm^2 on the right hemithorax whereas the corresponding values of the second measurement were 1,485.6 and 678.9 cm^2.

Respiratory Function

In 2003, respiratory function of 18 survivors—out of 23 subjects who had been examined in 1988–1990—was retested. The examined sample consisted of 14 men and 4 women (mean age 72.7 ± 6.5 years). In 1988, the plaque surface area was 11.27 ± 12.98 cm^2 (mean ± SD) and in 2003, increased to 18.06 ± 15.71 cm^2 (mean ± SD).

The findings of respiratory function measurements are presented in Table II.

In the first examination, we found that lung volumes and expiratory flow rates were within normal limits. In the present study, there was a considerable reduction of lung volumes; we have noticed a statistically significant decrease in TLC and FVC ($P < 0.001$) and a relative increase of expiratory flow rates since the %FEV_1 increased ($P < 0.01$).

Correlating change in plaque surface area with change in lung volume (TLC, FVC) and expiratory flow rates (%FEV_1, FEV_1), we found a statistically significant negative correlation ($r = -0.486$, $P = 0.041$, Fig. 5) between expansion in plaque surface area and reduction in TLC.

These findings (decrease in lung volumes combined with relative increase in expiratory flow rates) suggest that the restrictive ventilatory defect could be attributed to occult lung damage, since no obvious radiological abnormalities were detected in lung parenchyma.

Chest Neoplasms

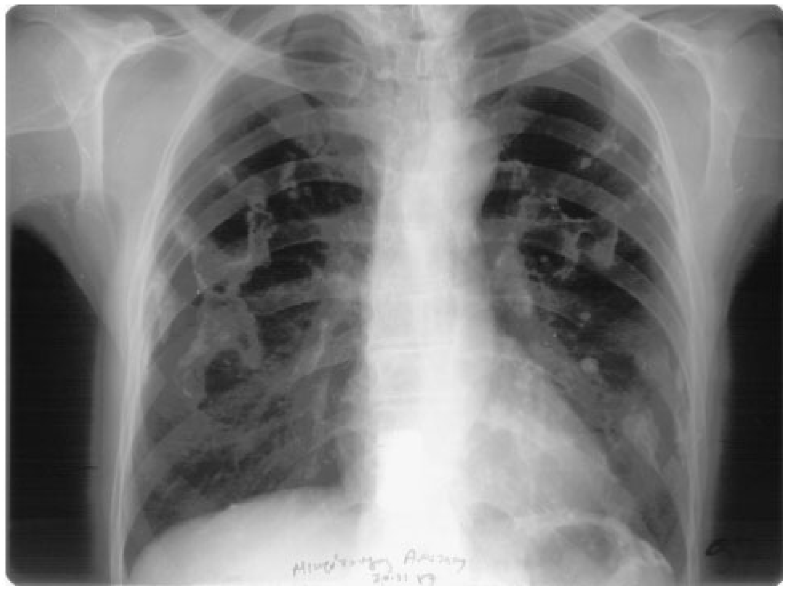
In the study population (198 subjects with pleural plaques), 4 cases of mesothelioma and 11 of malignant lung neoplasm were diagnosed during the follow-up period (1988–2003). At time of re-examination, all 15 patients were dead. All cases were males and all were smokers with the exception of one non-smoking woman.

DISCUSSION

Pleural plaques caused by environmental asbestos pollution require a long latency (over 40 years) period [Sichletidis et al., 1992a; Chapman et al., 2003] and may appear even if mild exposure to asbestos fibers occurs [Ehrlich et al., 1992]. Amphiboles are responsible for pleural plaques, and most environmental exposure is to tremolite, but there are areas of the world where other fibers (anthophyllite, crocidolite, and some other specific fibers) are responsible for pleural plaques [Chung and De Paoli, 1988; Sichletidis et al., 1992a; Rey et al., 1993; Hasanoglou et al., 2003].

A disadvantage of our first study [Sichletidis et al., 1992a] was the relatively low percentage of the target population (inhabitants over 40 years old) who agreed to participate. This was attributed to objective difficulties (voluntary participation, mountainous area, long distance between villages and center where examination took place, old age, and low educational level of participants). However, in the present study, we followed up only the group of people with pleural plaques. All survivors were examined.

According to the findings of this study, it is clear that radiological evidence of pleural plaques caused by asbestos environmental pollution is increasing, even if the exposure has ceased. Longitudinal studies in workers exposed to asbestos have revealed gradual deterioration in radiological picture of pleural plaques 20 years after the initial exposure [Ehrlich et al., 1992; Shepherd et al., 1997]. In a survey of 691 retired asbestos mine workers in South Africa, either a



b

FIGURE 2. Representative postero-anterior chest roentgenograms of a male subject at first (1988, 47.11 cm^2) (**a**) and at second examination (2003, 56.54 cm^2) (**b**). The expansion in the surface area of pleural plaques is clearly illustrated.

chest X-ray findings progressed or new ones developed, even though exposure ceased [Sluis-Cremer and Hnizdo, 1989].

Moreover, expansion of plaques was found to be greater on the left hemithorax. Other researchers [Withers et al., 1989; Hu et al., 1993] refer to similar findings, but a satisfactory explanation has not been given yet. However, the fact that the radiological lesions are usually more extensive on the left than on the right hemithorax has been challenged [Gallego, 1988].

As far as respiratory function is concerned, a decrease in lung volumes (TLC, FVC, RV), a slight decrease in FEV_1, and an increase in FEV_1/FVC ratio was found. A statistically significant negative correlation between decrease in TLC and increase in pleural plaques' surface area was observed. Pulmonary fibrosis has not been detected on chest X-rays of the persons studied but it is possible that a certain percentage of volume decrease may have resulted from radiologically occult parenchymatous damage. Therefore, in future studies more sensitive methods such as high-resolution computerized tomography (HRCT) should be used.

Respiratory function testing on people with pleural plaques has brought about contradictory results. Several

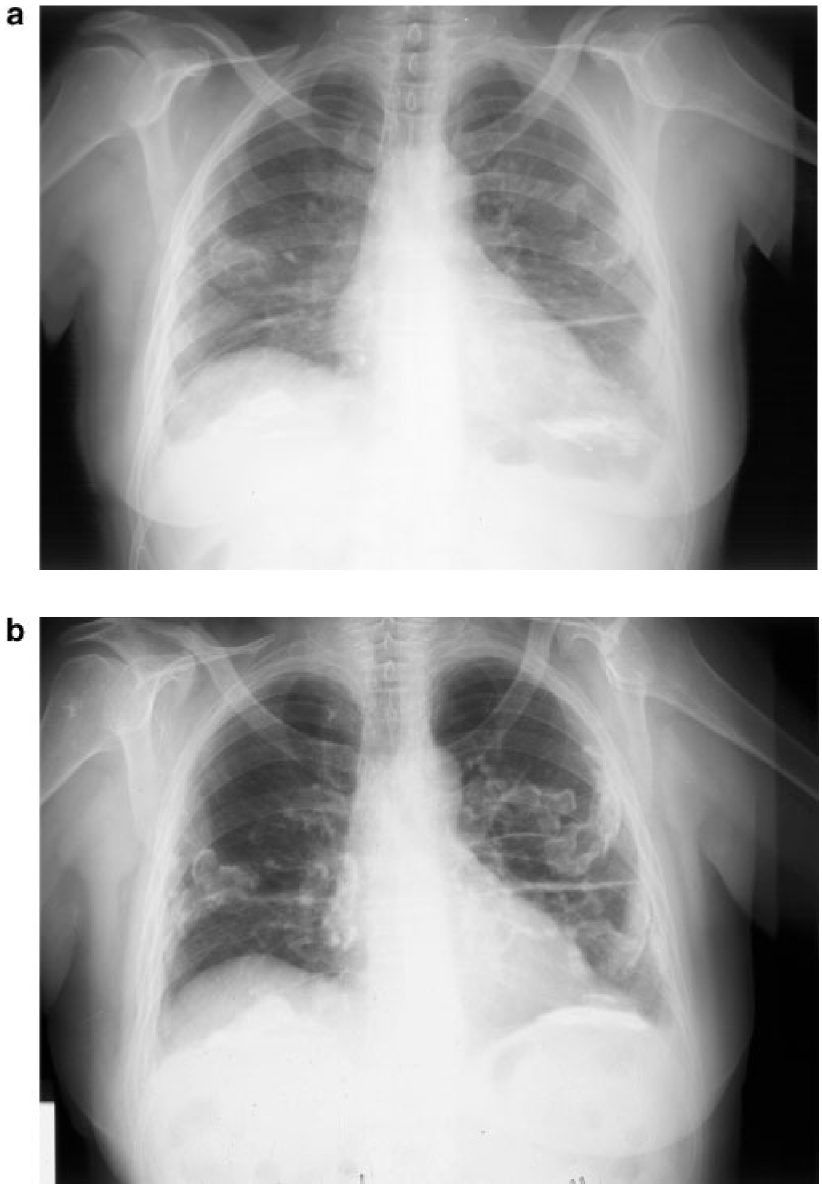


FIGURE 3. Representative postero-anterior chest roentgenograms of a female subject at first (1988, 25.08 cm^2) (**a**) and at second examination (2003, 69.59 cm^2) (**b**).

studies have concluded that there is no significant correlation between pleural plaques and respiratory function [Jones et al., 1980; Van Cleemput et al., 2001]. In a study from Belgium, 73 workers had been exposed to asbestos and cement for 23–27 years and no correlation has been found between presence or expansion of pleural plaques and respiratory function [Van Cleemput et al., 2001]. Nevertheless, some studies revealed that there was a slight influence of pleural plaques on respiratory function [Hillerdal et al., 1990; Schwartz et al., 1994], whereas in some others considerable worsening of respiratory function appeared [Jarvholm and Sanden, 1986; Kilburn and Warshaw, 1990]. According to Kilburn and Warshaw, FEV_1 and FVC significantly decreased in a sample of 155 non-smoking workers with pleural plaques compared to those not exposed to asbestos [Kilburn and Warshaw, 1990]. In contrast, there was a 6.9% decrease in FVC in 202 non-smoking shipyard-workers with pleural plaques, when compared to those without pleural plaques [Jarvholm and Sanden, 1986]. However, diffuse pleural thickening [Kouris et al., 1991; Rosenstock, 1991] seems to be more aggravating functionally than pleural plaques as it is present on both hemithoraxes [Schwartz et al., 1990].

The number of cases with mesothelioma found in our population (4 out of 198 people in 15 years' period) is about 1,300 times greater than the one expected which is 1/

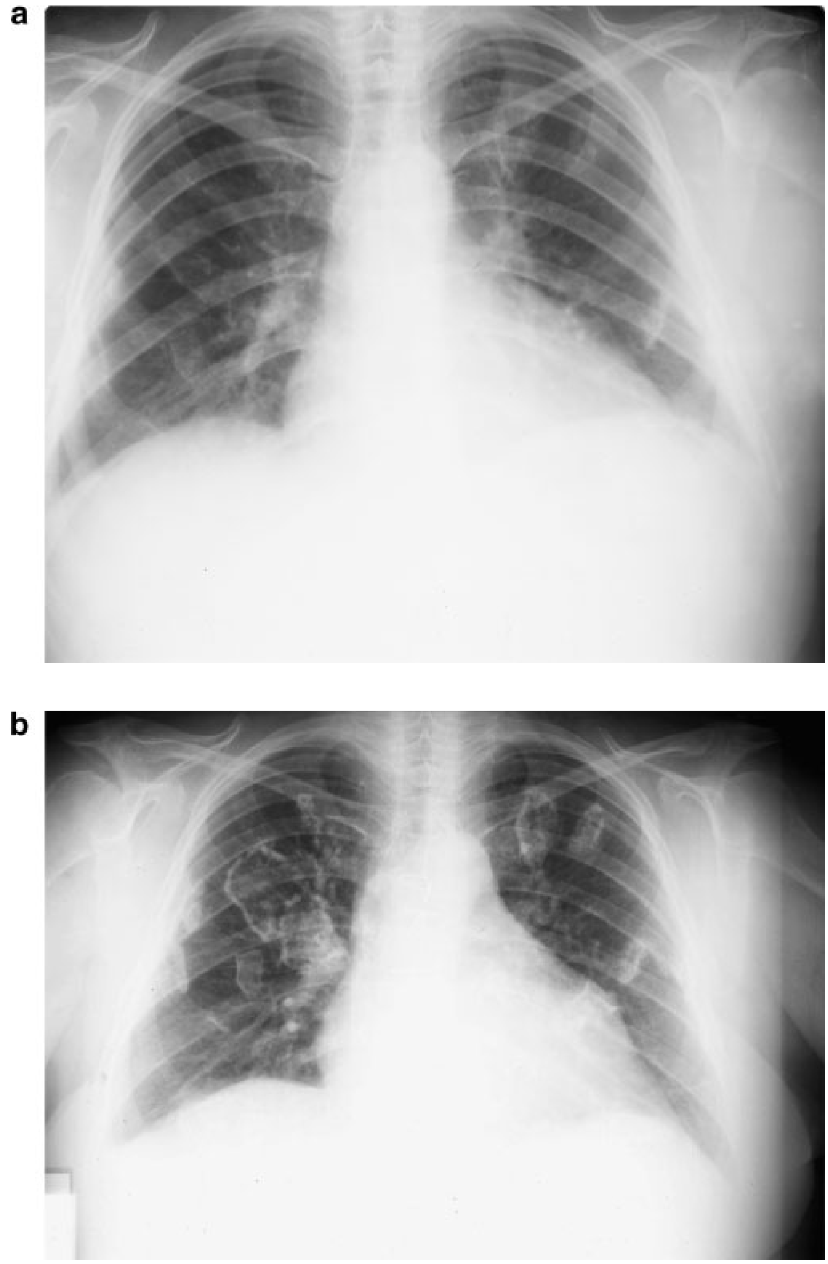


FIGURE 4. Representative postero-anterior chest roentgenograms of a female subject at first (1988, 7.35 cm^2) (**a**) and at second examination (2003, 52.78 cm^2) (**b**) showing considerable expansion in the surface area of pleural plaques.

1,000,000/year [Mc Donald, 1985], although real frequency of malignant mesothelioma in people not exposed to asbestos is probably even less [Hillerdal, 1999]. All these cases of mesothelioma were diagnosed in individuals with pleural plaques. Pleural plaques have been considered to be associated with high risk presence of malignant mesothelioma [Bianchi et al., 1997], even though an opposite opinion had been supported in the past [Constantopoulos et al., 1992]. From 1963 to 1985 in Upsala, Sweden, 1,598 men with pleural plaques were studied and it was found that relevant risk of developing lung cancer amounted to 1.4% while 9 cases of mesothelioma were diagnosed, compared to the 0.8 expected [Hillerdal, 1994]. The kind of the fibers (amphibole group, especially tremolite) plays an important role not only in the appearance of pleural plaques but also of mesothelioma caused by asbestos environmental exposure [Sichletidis et al., 1992b; Dumortier et al., 2002].

Unlike mesothelioma, chances of developing lung neoplasm are less [Hillerdal, 1994] and chrysotile fibers [Kishimoto et al., 2003] are primarily linked to blame for its

TABLE II. Results of Respiratory Function Measurement in 18 Subjects With Pleural Plaques, Residents of Almopia, Northern Greece in 1988 and 2003

	1988	2003	
TLC, l	5.55 ± 1.34	4.33 ± 0.88	
TLC %pred	95.65 ± 14.85	76.48 ± 9.26	$P < 0.001$
FVC, l	3.58 ± 0.93	2.77 ± 0.65	
FVC %pred	94.74 ± 17.98	80.12 ± 13.76	$P < 0.001$
RV, l	1.95 ± 0.55	1.52 ± 0.35	
RV %pred	98.15 ± 23.85	66.1 ± 13.48	$P < 0.001$
FEV_1, l/s	2.84 ± 0.71	2.36 ± 0.59	
FEV_1 %pred	93.43 ± 13.56	89.1 ± 10.84	$P < 0.01$
%FEV_1	79.84 ± 6.81	84.95 ± 6.48	$P < 0.01$

appearance; however, the role of smoking as co-existing carcinogenic factor cannot be easily excluded.

In conclusion, the radiological outcome of pleural plaques, in individuals that have been previously exposed to asbestos environmental pollution, worsens over the years in the same way as it does in patients with occupational exposure. Respiratory function is slightly affected by asbestos exposure, showing a mild restrictive ventilatory defect. Malignant mesothelioma prevalence is very high in persons studied and is mainly attributed to the high concentration of tremolite in asbestos rocks in the area studied. The present study provides evidence that pleural plaques due to asbestos environmental pollution expand over the years and that respiratory function of afflicted persons also deteriorates.

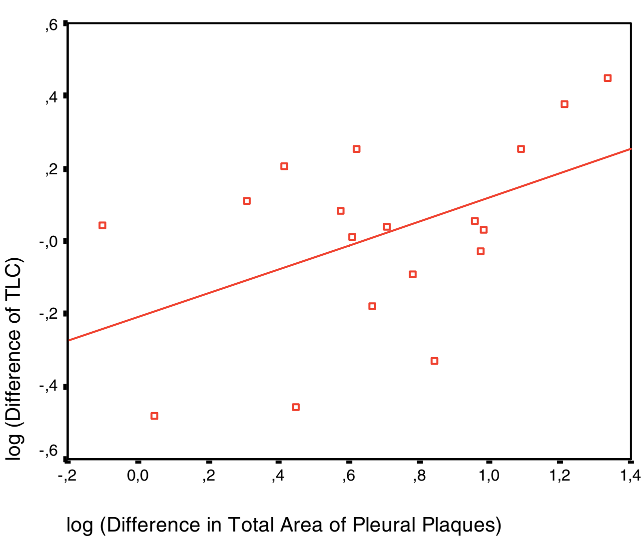


FIGURE 5. Scatter plot illustrating the linear relationship between decrease in total lung capacity (TLC) and increase in total area of pleural placques, after logarithmic transformation of variables' values. Pearson correlation coefficient: $r = -0.486$, $P = 0.041$.

REFERENCES

Baris YI, Artivinli M, Sakin AA. 1979. Environmental mesothelioma in Turkey. Ann NY Acad Sci 6:424–446.

Baris YI, Saracci R, Simonato L, Skidmore JW, Artivinli M. 1981. Malignant mesothelioma and radiological chest abnormalities in two villages in central Turkey. Lancet 1:984–987.

Bianchi C, Brollo A, Ramani L, Zuch C. 1997. Pleural plaques as risk indicators for malignant pleural mesothelioma: A necropsy-based study. Am J Ind Med 32:445–449.

Chapman SJ, Cookson WOC, Musk AW, Lee YCG. 2003. Benign asbestos pleural diseases. Curr Opin Pulm Med 9:266–271.

Chung A, De Paoli L. 1988. Environmental pleural plaques in residents of Quebec chrysotile mining town. Chest 94:58–60.

Constantopoulos SH, Goudevenos JA, Saratzis N, Langer Am, Selikoff IJ, Moutsopoulos HM. 1985. Metsovo lung: Pleural calcifications and restrictive lung function in Northwestern Greece. Environmental exposure to mineral fiber as etiology. Environ Res 38:319–331.

Constantopoulos SH, Dalavanga YA, Sakellariou K, Goudevenos J, Kotoulas OB. 1992. Lymphocytic alveolitis and pleural calcifications in nonoccupational asbestos exposure. Protection against neoplasia? Am Rev Respir Dis 146:1565–1570.

Crapo RO, Morris AH, Clayton PD, Nixon CR. 1982. Lung volumes in healthy nonsmoking adults. Bull Eur Physiopathol Respir 18:419–425.

Dumortier P, Rey F, Viallat JR, Broucke I, Boutin C, De Vuyst P. 2002. Chrysotile and tremolite asbestos fibers in the lungs and parietal pleura of Corsican goats. Occup Environ Med 59:643–646.

Ehrlich R, Lilis R, Chan E, Nicholson WJ, Selikoff IJ. 1992. Long term radiological effects of short term exposure to amosite asbestos among factory workers. Br J Ind Med 49:268–275.

Gallego JC. 1988. Absence of left-sided predominance in asbestos-related pleural plaques. Chest 113:1034–1036.

Hasanoglou HC, Gokirmak M, Baysal T, Yildirim Z, Koksal N, Onal Y. 2003. Environmental exposure to asbestos in Eastern Turkey. Arch Environ Health 58:144–150.

Hillerdal G. 1986. Endemic pleural plaques. Eur J Respir Dis 69:1–3.

Hillerdal G. 1994. Pleural plaques and risk for bronchial carcinoma and mesothelioma. A prospective study. Chest 105:144–150.

Hillerdal G. 1999. Mesothelioma: Cases associated with non-occupational and low dose exposures. Occup Environ Med 56:505–513.

Hillerdal G, Malmberg P, Hemmingsson A. 1990. Asbestos-related lesions of the pleura: Parietal plaques compared to diffuse thickening studied with chest roentgenography, computed tomography, lung function, and gas exchange. Am J Ind Med 18:627–639.

Hu H, Beckett L, Kelsey K, Christiani D. 1993. The left-sided predominance of asbestos-related pleural disease. Am Rev Respir Dis 148:981–984.

Jarvholm B, Sanden A. 1986. Pleural plaques and respiratory function. Am J Ind Med 10:419–426.

Jones RN, Diem JE, Glindmeyer H, Weill H, Gilson JC. 1980. Progression of asbestos radiographic abnormalities: Relationships to estimates of dust exposure and annual decline in lung function. IARC Sci Publ 30:537–543.

Kilburn KH, Warshaw R. 1990. Pulmonary functional impairment associated with pleural asbestos disease. Circumscribed and diffuse thickening. Chest 98:965–972.

Kishimoto T, Ohnishi K, Saito Y. 2003. Clinical study of asbestos-related lung cancer. Ind Health 41:94–100.

Kouris SP, Parker DL, Bender AP, Williams AN. 1991. Effects of asbestos-related pleural disease on pulmonary function. Scan J Work Environ Health 17:179–183.

Langer AM, Constantopoulos SH, Nolan RP, Moutsopoulos HM. 1987. Association of Metsovo lung and pleural mesothelioma with exposure to tremolite-containing whitewash. Lancet 1:965–967.

Mc Donald JC. 1985. Health implications of environmental exposure to asbestos. Environ Health Perspect 62:319–328.

Rey F, Boutin C, Steinbauer J, et al. 1993. Environmental pleural plaques in an asbestos exposed population of Northeast Corsica. Eur Respir J 6:978–982.

Rosenstock L. 1991. Roentgenographic manifestations and pulmonary function effects of asbestos-induced pleural thickening. Toxicol Ind Health 7:81–87.

Schwartz DA, Fuortes LJ, Galvin JR, et al. 1990. Asbestos induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 141:321–326.

Schwartz DA, Davis CS, Merchant JA, et al. 1994. Longitudinal changes in lung function among asbestos-exposed workers. Am J Respir Crit Care Med 150:1243–1249.

Shepherd JR, Hillerdal G, McLarty J. 1997. Progression of pleural and parenchymal disease on chest radiographs of workers exposed to amosite asbestos. Occup Environ Med 54:410–415.

Sichletidis L, Daskalopoulou E, Chloros D, Vlachogiannis E, Vamvalis C. 1992a. Pleural plaques in a rural population in Central Macedonia, Greece. Med Lav 83:259–265.

Sichletidis L, Daskalopoulou E, Tsarou V, Pnevmatikos I, Chloros D, Vamvalis C. 1992b. Five cases of pleural mesothelioma with endemic pleural calcifications from a rural area in Greece. Med Lav 83:326–329.

Sluis-Cremer GK, Hnizdo E. 1989. Progression of irregular opacities in asbestos miners. Br J Ind Med 46:846–852.

Van Cleemput J, De Raeve H, Verschakelen JA, Rombouts J, Lacquet LM, Nemery B. 2001. Surface of localized pleural plaques quantitated by computed tomography scanning: No relation with cumulative asbestos exposure and no effect on lung function. Am J Respir Crit Care Med 163:705–710.

Withers BF, Ducatman AM, Yang WN. 1989. Roentgenographic evidence for predominant left-sided location of unilateral pleural plaques. Chest 95:1262–1264.